

*S4 Table. Association between a 4-level affinity classification based on predicted  $\Delta\Delta G$  with high- and low- binding RBD binding ACE2 variants identified by deep mutagenesis.*

mCSM-PPI2 (kcal mol <sup>-1</sup> )	nCoV-S High sorts log <sub>2</sub> enrichment ratio		recal. mCSM-PPI2 (kcal mol <sup>-1</sup> )	nCoV-S High sorts log <sub>2</sub> enrichment ratio	
	<u>&lt; 0</u>	<u>&gt;= 0</u>		<u>&lt; 0</u>	<u>&gt;= 0</u>
< -1	105	5	< -1	108	5
(-1, 0]	199	67	(-1, 0]	127	36
(0, 1]	45	12	(0, 1]	106	40
>= 1	2	2	>= 1	10	5
$\chi^2 = 23$ , p = 0.00003			$\chi^2 = 24$ , p = 0.00002		